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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/696,909	LORENS ET AL.	
	Examiner	Art Unit	
	Peter J. Reddig	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12,14-18,27,40-44,54 and 55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 12, 14-18, 27, 40-44, 54, and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 30, 2007 has been entered.

2. An action on the RCE follows.

3. Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are pending.

4. Claims 27 and 40-44 have been rejoined for examination as they are now drawn to the originally elected species of *in vitro* as the location of identification of a compound that inhibits angiogenesis.

5. Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are currently under consideration as drawn to *in vitro* as the location of identification of a compound that inhibits angiogenesis.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and its dependent claims, 12 and 14-18, are indefinite because the second step of claim 1 is drawn to a cell-based angiogenesis phenotype assay an endothelial cell comprising *the* angiogenesis polypeptide (emphasis added). Given that step two of claim 1 is an independent assay from that of step 1 it is unclear if the angiogenesis polypeptide of step 2 is drawn to using the angiogenesis polypeptide of step 1 or another angiogenesis polypeptide. Thus the metes and bounds of the claims cannot be determined. Amendment of claim 1 to replace the term "the" with the term "said" would clarify the claim and obviate the instant grounds of rejection.

Additionally, step 2 of claim 1 is drawn to "... wherein inhibition of the angiogenesis polypeptide in the *in vitro* kinase activity..." and it is unclear as to what inhibition in the *in vitro* kinase activity is. Amendment of the claims to "wherein inhibition of the *in vitro* kinase activity of the angiogenesis polypeptide" would obviate this objection.

Furthermore, step 2 of claim 1 does not require that the endothelial cell present with an angiogenesis phenotype, thus how can the angiogenesis phenotype be inhibited if no angioenesis phenotype is present? Amendment of step 2 of claim 1 to "performing a cell-based angiogenesis phenotype assay using an endothelial cell having an angiogenesis phenotype" would obviate this rejection.

Furthermore, claim 27 does not require that the endothelial cell contacted with a compound have an angiogenesis phenotype, thus how can the angiogenesis phenotype assay be inhibited if no angioenesis phenotype is present? Thus claims 27 and its dependent claims are indefinite. Amendment of step 1 of claim 27 to "contacting the compound with an endothelial cell that has an angiogenesis phenotype" would obviate this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 12, 14-18, 27, 40-44, 54, and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Given the indefinite nature of claim 1, it is assumed for examination purposes that "the angiogenesis polypeptide" of step 2 of claim 1 is drawn to an Axl/ angiogenesis polypeptide with greater than 95 % identity to SEQ ID NO: 4.

The claims are drawn to identifying compounds that inhibit angiogenesis by identifying compounds that inhibit the in vitro kinase activity of an Axl/angiogenesis polypeptide, inhibits

the angiogenesis phenotype of an Axl/angiogenesis polypeptide in a cell based phenotype assay, or down regulates an Axl polypeptide.

The specification teaches that a functional genetic screening strategy was used to identify proteins involved in regulating endothelial cell migration on specific matrix components, e.g. vitronectin, by stably expressing complex libraries of various types of genetic elements (e.g. cDNAs and GFP-fusions) in human primary endothelial cells (e.g. HUVECs) with a retroviral-based system, p. 5 lines 3-7. The specification teaches that the migration of activated endothelial cells through a vitronectin-rich provisional matrix is critical to the formation of new blood vessels during angiogenesis and is dependent on adhesion receptors containing alpha V integrins (such as alphaVbeta3 which binds to vitronectin), p. 1, lines 22-25. Using this method cells were selected for impaired haptotaxis, Example 1, p. 48, lines 23-30. The specification teaches in Figure 11 that Axl was identified as an antisense hit in this assay.

The specification teaches that treatment of HUVEC cells with RNAi directed to Axl inhibits the haptotaxis, proliferation, and tube formation in HUVEC cells *in vitro*, see Figures, 13, 14, 15, and 17.

One cannot extrapolate the teaching of the specification to the enablement of the claims because the art teaches that Axl activation inhibits angiogenesis and the Applicants argue that the inhibition of Axl would stimulate angiogenesis.

In particular, Galliccio et al. (Blood, 1 March 2005, Vol. 105, No. 5, pp. 1970-1976, previously cited) teaches that the interaction of Gas-6 with Axl activates Axl and inhibits VEGF-dependent angiogenesis, see Abstract, Figures 1and 3 and Table 1.

Furthermore Applicants state on page 14, 3rd para of the Remarks of 10/05/2007 "Gallicio *et al.* discloses that Gas-6 **stimulates** the Axl polypeptide, which inhibits activation of vascular endothelial growth factor receptor 2 (VEGF-R2), which, thus, **inhibits activation** of an angiogenic program in vascular endothelial cells. Based on the results of Gallieio *et al.*, those of skill would predict that **inhibition** of the Axl peptide would activate VEGF-R2 and **stimulate activation** of an angiogenic program in vascular endothelial cells. At a minimum, those of skill would predict that inhibition of the Axl polypeptide would have little or no effect on an angiogenesis program based on the results of Gallicio *et al.*" Given that activation of Axl inhibits angiogenesis and Applicants argue as such, one of skill in the art would not believe it more likely than not the identification of compounds that inhibit Axl kinase activity or down-regulate Axl would lead to the identification of compounds that inhibit angiogenesis.

Although Applicants provide evidence that down-regulation of Axl inhibits haptotaxis, proliferation, and tube formation in HUVEC cells in vitro, the unpredictability of extrapolating the results of in vitro drug assays to in the vivo response of cells and tissues is well known in the art.

In particular Zips et al (In vivo, 2005, 19:1-7) specifically teach that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.*

Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col 2). Furthermore, as drawn to angiogenesis in particular, Hanahan and Folkman (Cell, 1996, 86: 353-364, 1996) teach that the process of angiogenesis in an *in vivo* situation is a complex process involving multiple factors (page 353, introduction). Hanahan and Folkman teach that it involves the motility of the endothelial cells, their interaction and modulation of the extracellular matrix, changes in the architecture of the endothelial cells, and their regulation of numerous growth and inhibitory factors. Furthermore, Fràter-Schröder et al. (Proc. Natl. Acad. Sci. USA, 1987, 84:5277) teach that tumor necrosis factor α effectively inhibits endothelial cell proliferation *in vitro* tissue culture assays, but does not inhibit angiogenesis in *in vivo* assays (see, abstract and introduction, p. 5277) demonstrating that *in vitro* assays do not recapitulate the full scope of angiogenesis *in vivo*.

Thus, given that the art teaches and Applicants argue that activation of Axl inhibits angiogenesis and given that the data presented on the effects of down-regulation of Axl in the specification is based on in vitro cell culture data, one of skill in the art would not believe it more likely than not that the claimed inventions would function as claimed, that is in the identification of inhibitors of angiogenesis based upon the identification of compounds that inhibit the function or expression of an Axl, angiogenesis peptide *in vitro*, without undue experimentation.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA

1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claims 1, 12, 14-18 and 55 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claim 1 for identifying a compound that inhibits angiogenesis, in which the angiogenesis/AXL polypeptide is SEQ ID NO: 4, *does not* reasonably provide enablement for the method of claim 1 for identifying a compound that inhibits angiogenesis, in which the angiogenesis/AXL polypeptide

comprises an amino acid sequence with greater than 95% identity to SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Given the indefinite nature of claim 1, it is assumed for examination purposes that "the angiogenesis polypeptide" of step 2 of claim 1 is drawn to an Axl, angiogenesis polypeptide with greater than 95 % identity to SEQ ID NO: 4.

The claims are broadly drawn to the methods of claim 1 and 27 for identifying a compound that inhibits angiogenesis, in which the angiogenesis/AXL polypeptide comprises an amino acid sequence with greater than 95% identity to SEQ ID NO: 4.

One cannot extrapolate the teachings of the specification to enable the scope of the claims in view of the multiple variants contemplated for the Axl, angiogenesis polypeptide and given that step 2 of claim 1 is not limited to any angiogenesis polypeptide and because the unpredictability of protein biochemistry is well known in the art.

In particular, Bowie et al (Science, 1990, 257:1306-1310, previously cited) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990, previously cited) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252, previously cited) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. In view of the unlimited and undefined alteration in the Axl, angiogenesis polypeptide contemplated in the specification and claimed, the

function of the broadly claimed Axl, angiogenesis polypeptide would not be expected to be the same as that of an unaltered Axl, angiogenesis polypeptide and the effects of modulators of the claimed protein could not be extrapolated to effects on SEQ ID NO: 4 with a reasonable expectation of success. Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al the effects of undefined changes in the Axl, angiogenesis polypeptide on the cell based angiogenesis assay could not be predicted. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence

has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Some of Applicants' arguments in the Remarks of October 5, 2007 are germane to the instant rejection.

Applicants argue that support for the protein with 95% identity to full length SEQ ID NO: 4 is provided by SEQ ID NO: 4, the fact the Axl is well known and sequence algorithms and kinase assays can be used to identify polypeptides that fall within the scope of the claims. Applicants argue that down regulation of Axl polypeptide results in an inhibition of a number of cell-based angiogenesis assays.

Applicants arguments have been considered, but have not been found persuasive because the issued raised here is that the unpredictability of predicting protein function from protein structutre and although Axl is well known in the art Applicants have not taught the amino acids of Axl that are crtical for it to functionin in the claimed method using kinase assays and a cell based angiogenesis phenotype assay. Although Applicant might argue that one of ordinary skill could screen for the species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants reiterate arguments drawn to Sun and Bandman. The arguments were previously considered and not found persuasive for the reasons of record.

Applicants arguments have been considered, but have not been found persuasive because the claims are not limited to the angiogenesis polypeptide with greater than 95% identity to full length SEQ ID NO: 4 for the reasons set forth above and thus the claims are not enabled for the reasons set forth above. Furthermore, the citations of Sun at page 7 and Bandman at page 15 do not appear to be relevant to the instant rejection in that Sun at page 7 is simply a summary of the arguments and Bandman at page 15 is just an address.

Applicants argue that claim 1 has been amended to include the step of inhibition of a cell-based angiogenesis phenotype assay in the presence of the compound to provide a nexus between the down regulation of Axl and angiogenesis.

Applicants arguments have been considered, but have not been found persuasive because the claims are not limited to SEQ ID NO:4 and thus are not enabled for the reasons set forth previously and above do not provide a nexus between the claimed angiogenesis polypeptide and angiogenesis

9. If Applicants were able to overcome the rejections set forth above under 35 U.S.C. 112, first paragraph, claims 27, 40-44, and 54 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an endothelial cell that expresses an Axl polypeptide, SEQ ID NO:4, wherein said cell displays an angiogenesis phenotype wherein down regulation of said Axl polypeptide inhibits an angiogenesis phenotype in an cell-based-angiogenesis phenotype assay; and (ii) determining if the *compound downregulates said Axl polypeptide*, thereby identifying the compound that inhibits angiogenesis, *does not* reasonably provide enablement for an *in vitro*

method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an endothelial cell that expresses an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence *with greater than 95% identity to full length of* SEQ ID NO:4 and wherein down regulation of the Axl polypeptide inhibits a cell-based angiogenesis phenotype assay; and (ii) *determining the functional effect* of the compound upon the Axl polypeptide, thereby identifying the compound that inhibits angiogenesis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to an *in vitro* method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an endothelial cell that expresses an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence *with greater than 95% identity to full length of* SEQ ID NO:4 and wherein down regulation of the Axl polypeptide inhibits a cell-based angiogenesis phenotype assay; and (ii) *determining the functional* effect of the compound upon the Axl polypeptide, thereby identifying the compound that inhibits angiogenesis.

This means that the claims encompass a method for identifying a compound that inhibits angiogenesis using an endothelial that express any Axl polypeptide with greater than 95% identity to full length SEQ ID NO: 4 in the cell based angiogenesis phenotype assay and determining *any* functional effect upon the Axl polypeptide to identify the compound that inhibits angiogenesis.

The specification teaches as set forth above.

Additionally, the specification teaches that RNAi to Axl reduces Axl protein levels, inhibits haptotaxis, inhibits proliferation, and inhibits endothelial tube formation in primary human endothelial cells (HUVEC), see Figures 11-15 and 17.

Furthermore, Applicant notes in the Remarks of 10/05/07 (p. 10, 1st para.) that "The claimed methods have already identified inhibitors of the Axl polypeptide that also inhibit angiogenesis. Down regulation of the Axl polypeptide by an inhibitory molecule and the resulting inhibition era number of cell-based angiogenesis assays is demonstrated at Figures 12-17".

The specification also teaches that the phrase "functional effects" in the context of assays for testing compounds that modulate activity of an angiogenesis and tumorigenesis protein includes the determination of a parameter that is indirectly or directly under the influence of an angiogenesis polypeptide, e.g., a chemical or phenotypic effect such as loss-of angiogenesis or tumorigenesis phenotype represented by a change in expression of a cell surface marker $\alpha V\beta 3$ integrin, changes in cellular migration, changes in endothelial tube formation, and changes in tumor growth, or changes in cellular proliferation, especially endothelial cell proliferation; or enzymatic activity; or, e.g., a physical effect such as ligand binding or inhibition of ligand binding. A functional effect therefore includes ligand binding activity, the ability of cells to proliferate, expression in cells undergoing angiogenesis or tumorigenesis, and other characteristics of angiogenic and tumorigenic cells. "Functional effects" include in vitro, in vivo, and ex vivo activities, p. 8, lines 15-26. Additionally, it is noted that the specification teaches that "determining the functional effect" means assaying for a compound that increases or decreases a parameter that is indirectly or directly under the influence of an angiogenesis protein,

e.g., measuring physical and chemical or phenotypic effects. Such functional effects can be measured by any means known to those skilled.

One cannot extrapolate the teachings of the specification to enable the scope of the claims because no nexus has been established between the broadly claimed Axl polypeptide, the down regulation of said polypeptide and inhibiting angiogenesis because the unpredictability of protein biochemistry is well known in the art.

In particular, Bowie et al (Science, 1990, 257:1306-1310, previously cited) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990, previously cited) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252,

previously cited) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, given the teachings of Bowie et al, Lazar et al, and Burgess et al the effects of undefined changes on the function of the broadly claimed Axl polypeptide would not be expected to be the same as that of an unaltered Axl polypeptide and the effects of modulators of the claimed protein in the cell based angiogenesis assay could not be extrapolated to effects on SEQ ID NO: 4 with a reasonable expectation of success. Thus, it would take undue experimentation for one of ordinary skill in the art to practice the invention as claimed.

Additionally, one cannot extrapolate the teachings of the specification to the scope of the claims because it is clear from the teachings of the specification and Applicants' remarks that the specification has only established an nexus *in vitro* between down regulation of Axl/SEQ ID NO: 4 and inhibition of angiogenesis and not between angiogenesis and any of the other functional effects on Axl/ SEQ ID NO: 4 contemplated in the specification or claimed. Furthermore, it is well known in the identification of novel angiogenesis and cancer therapeutics (as is the clearly contemplated use for the claimed method, see p. 2, lines 5-22) is unpredictable.

In particular, Gura (Science, 1997, 278:1041-1042, previously cited) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29

have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313:1370, previously cited) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Additionally, Clamp and Jayson (British Journal of Cancer, 2005 93:967-972, previously cited) teach that the despite activity of the angiogenesis inhibitor endostatin in animal models, the clinical trial results were disappointing and only minor responses were observed (see Abstract and p. 969, left col.).

Given the unpredictability of the art of developing novel therapeutics, given that no nexus has been established between any functional effect on Axl/ SEQ ID NO:4, except for down regulation of Axl/SEQ ID NO:4 in vitro, and given that the Applicant states that downregulation of Axl results in the inhibition of angiogenesis, one of skill in the art would could not predictably extrapolate the teachings of the specification to scope of the claims, where one can determine any functional effect on the angiogenesis polypeptide to identify a compound that inhibits angiogenesis.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the

invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. Claims 1, 12, 14-18, 27, 40-44 and 55 are rejected under 35 USC 112, first paragraph, as lacking an adequate written description in the specification.

Claims 1, 12, 14-18 and 55 are broadly drawn to a method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i)determining, in the presence and absence of the compound, in vitro kinase activity of an angiogenesis polypeptide comprising an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 95% identity to full length SEQ ID NO:4 and wherein the angiogenesis polypeptide has kinase activity in the absence of said compound; and (ii) performing a cell-based angiogenesis phenotype assay using an endothelial cell comprising the angiogenesis polypeptide in the presence and absence of the compound, wherein inhibition of the angiogenesis polypeptide in the in vitro kinase activity and inhibition of the angiogenesis phenotype in the cell-based angiogenesis assay in the presence of the compound identifies the compound as a determining

the functional effect of the compound upon the angiogenesis polypeptide, thereby identifying the compound that inhibits angiogenesis.

Given the indefinite nature of claim 1, it is assumed for examination purposes that "the angiogenesis polypeptide" of step 2 of claim 1 is drawn to an Axl/ angiogenesis polypeptide with greater than 95 % identity to SEQ ID NO: 4.

Claims 27 and 40-44 are broadly drawn to an *in vitro* method for identifying a compound that inhibits angiogenesis, the method comprising the steps of: (i) contacting the compound with an endothelial cell that expresses an Axl polypeptide, wherein the Axl polypeptide comprises an amino acid sequence with greater than 95% identity to full length of SEQ ID NO:4 and wherein down regulation of the Axl polypeptide inhibits a cell-based angiogenesis phenotype assay; and (ii) determining the functional effect of the compound upon the Axl polypeptide, thereby identifying the compound that inhibits angiogenesis.

The state of the art is such that it is well know in the art that protein biochemistry is unpredictable and, thus, predicting protein function from structure is unpredictable.

In particular, Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col. 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid

substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Thus, given the above, it is clear that in the protein biochemistry arts an adequate written description is essential for one of skill in the art to make and use the claimed inventionand it is clear that the specification does not provide a written description of the broadly claimed invention for the reasons set forth below.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the

claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics.... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis, per Lilly by structurally describing a representative number of Axl/angiogenesis polypeptides with greater than 95% identity to SEQ ID NO: 4 that are useful for identifying a compound that inhibits angiogenesis or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis, nor does the specification provide any partial structure of the angiogenesis polypeptide that is

useful for identifying a compound that inhibits angiogenesis, nor any physical or chemical characteristics of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses Axl/SEQ ID NOs: 4 and 6 this does not provide a description of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis that would satisfy the standard set out in Enzo.

The specification also fails to describe the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis by the test set out in Lilly. The specification describes only two angiogenesis /Axl polypeptides. Therefore, it necessarily fails to describe a "representative number" of species of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that are useful for identifying a compound that inhibits angiogenesis. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of the Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention. Since the specification fails to adequately describe or reasonably convey to one skilled in the relevant art

that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention that is the broadly claimed Axl/angiogenesis polypeptide with greater than 95% identity to SEQ ID NO: 4 that is useful for identifying a compound that inhibits angiogenesis, it also fails to adequately describe the claimed method or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Some of Applicants' arguments in the Remarks of October 5, 2007 are germane to the instant rejection.

Applicants argue that the specification does provide descriptive support for the full scope of the claimed invention by providing both SEQ ID NO: 4, a reference sequence for the recited polypeptides, and assays for regulation and inhibition of angiogenesis. Applicants argue that Axl kinase activity was well known at the time of filing. Applicants argue that the assays are described throughout the specification and thus the information in the specification to meet the written description requirment, particularly in view of Enzo, recent Board decision, and the USPTO's written description guidelines.

Applicants arguments have been considered, but have not been found persuasive because Applicants have not taught the amino acids of Axl that are crtical for it to functionin in the claimed method using kinase assays and a cell based angiogenesis phenotype assay. Although Applicant might argue that one of ordinary skill could screen for the species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not

sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

Applicants reiterate arguments drawn to Sun and Bandman. The arguments were previously considered and not found persuasive for the reasons of record.

Applicants argue that the Office Action also disputes that Example 14 of the Synopsis of Application of Written Description Guidelines applies to the claims. In response, Applicants argue that the amended claims recite kinase activity of the Axl protein and an assay for inhibition of an angiogenesis phenotype caused by the inhibition of the Axl protein. The Synopsis indicates that a "single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay.... "that could be used to identify members of the claimed genus. The amended claims thus follow the guidelines for written description put forth by the US Patent Office.

Applicants arguments have been considered, but have not been found persuasive because Applicants have given no teaching or direction as to which amino acid residues can be predictably altered so that the polypeptide will function as claimed and, thus, for the reasons set forth above the specfication fails to provide an adequate written description.

11. Claims 1, 12, 14-18, 54, 27, 40-44, 54 and 55 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. Currently amended claim1, and thus its dependent claims, have no clear support in the specification and the claims as originally filed. Applicants argue that support for amended Claim 1 is found throughout the specification, for example, at page 6, lines 7-20. Claim 1 is also amended to recite performance of assays in the presence and absence of the test compound.

Support for this amendment is found throughout the specification, for example, at page 9, line 32 through page 10, line 4. Claim 1 is also amended to recite a step of performing a cell based angiogenesis phenotype assay using a cell that comprises the Axl angiogenesis polypeptide. Support for this amendment is found throughout the specification, for example, at page 8, lines 18-24, page 30, lines 6-10 and 14-29, page 31, line 22 through page 33, line 12, and page 32, lines 25-26. Claim 1 is further amended to recite that inhibition of Axl kinase activity and inhibition of the cell- based angiogenesis phenotype assay in the presence of the compound identify the compound as an inhibitor of angiogenesis. Support for this amendment is found throughout the specification, for example, at Figures 12-17, which demonstrate that an RNAi molecule specific for the nucleic acid that encodes the Axl angiogenesis polypeptide down regulates expression of the Axl polypeptide in a cell and that down regulation and lack of expression of the Axl polypeptide causes inhibition of cell-based angiogenesis assays. As expression of the Axl polypeptide is down regulated, kinase activity of the Axl polypeptide is also necessarily down regulated in the cell.

A review of the specification discloses support for Axl, its ligands, expression, and association with diseases (page 6, lines 7-20), a general description of an assay to identify inhibitors of angiogensis/tumorigenes (page 9, line 32 through page 10, line 4), the definition of "functional effect" described *supra* (page 8, lines 18-24), a general description of assessing the modulation of an angiogenesis protein (page 30, lines 6-10), numerous assays to measure angiogenesis associated with tumors, tumor growth, neovascularization, endothelial tube 25 formation, cell surface markers such as alpha V beta 3, hormone release, transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), changes in cell

metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as cGMP. In one embodiment, measurement of integrin cell surface expression and FACS sorting is used to identify modulators of angiogenesis, (page 30, lines 14-29), measuring ligand binding, cell surface marker expression, cellular proliferation, VEGF-R assays, co-culture assays for tube formation, cell migration assays, mRNA or protein expression, haptotaxis, tube formation, CAM assays, cellular morphology (e.g., cell volume, nuclear volume, cell perimeter, and nuclear perimeter), ligand binding, kinase activity, apoptosis, cell surface marker expression, cellular proliferation, GFP positivity and dye dilution assays (e.g., cell tracker assays with dyes that bind to cell membranes), DNA synthesis assays, and cell cycle arrest, (page 31, line 22 through page 33, line 12, and page 32, lines 25-26), treatment of HUVEC cells with RNAi directed to Axl inhibits the haptotaxis, proliferation, and tube formation in HUVEC cells *in vitro* (figures 12-17) The suggested support is not found persuasive because there is nothing in the specification to suggest the specific combination of assay steps in claim 1 to identify a compound that inhibits angiogenesis.

Additionally, the teachings of the specification do not support an Axl polypeptide with "greater than" 95% identity to full length SEQ ID NO: 4, only "greater than about" 95% identity as described in claims 1 and 27, para. bridging p. 7 and 8. Furthermore, there is nothing in the specification or claims as originally filed to support an Axl polypeptide comprising SEQ ID NO:4, which encompasses sequences outside of SEQ ID NO: 4.

Thus the subject matter claimed in claims 1, 12, 14-18, 27, 40-44, 54 and 55 broadens the scope of the invention as originally disclosed in the specification and claims as originally filed.

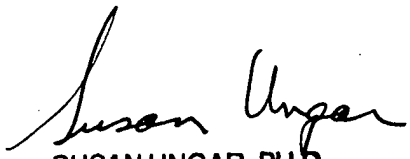
12. All other objections and rejections previously set forth in the office action of May 7, 2007 are withdrawn.

13. No claims allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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